Objectives

- Describe pharmacokinetic and pharmacodynamic differences associated with pregnancy and lactation and how these affect medication distribution
- Discuss the metabolic differences with neonatal patients as compared to pediatric and adult patients
- Review appropriate dosing in pediatric patients
- Identify issues with medication administration in children and potential solutions
- Understand the reasoning behind why medication problems are greater in children and identify safe practice recommendations

Outline

- Drug Disposition & Dosing
  - Pregnancy & Lactation
  - Neonates & Infants
  - Children & Adolescents
  - Medication Administration Issues in Pediatric Patients
  - Medication Related Problems
  - Safe Medication Practices & Recommendations

Prescription Drug Use in Pregnancy

- Nearly 60 million women in the U.S. of childbearing age
- 1 of 10 women get pregnant each year
- 64% of pregnant women use at least one prescription drug

Physiologic Changes in Pregnancy

- Increase in total body weight and body fat
- Delayed gastric emptying
- Increased plasma volume by 30-50%
- Decrease in plasma albumin
- Increased glomerular filtration rate
- Increased organ blood flow
- Changes in hepatic enzyme activity

Pharmacologic Considerations in Pregnancy

- Treating two individual patients
  - Differences in pharmacokinetics and pharmacodynamics
  - Prescription and non-prescription medications
  - Assessment of risk/benefit
  - Effectively treat without adverse effects to fetus
Pharmacologic Considerations in Pregnancy-Placental Drug Transfer

- Placental passage
  - Protein binding
  - Lipid solubility
  - Ionization constant (pKa)

- Fetal exposure
  - Maternal pharmacokinetics
    - Volume of distribution
    - Rate of metabolism
    - Excretion by placenta
  - Drugs which will not cross the placenta
    - High molecular weight
    - Ionized
    - Hydrophilic

Pregnancy Risk Categories

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate and well-controlled studies in pregnancy women show no risk to the fetus</td>
</tr>
<tr>
<td>Animal studies failed to show risk to the fetus; no studies in pregnant women</td>
</tr>
<tr>
<td>Animal studies show adverse effects to the fetus; no studies in pregnant women benefits of use must outweigh risk</td>
</tr>
<tr>
<td>Possible evidence of human fetal risk; risk of use must outweigh benefit</td>
</tr>
<tr>
<td>Animal or human studies shown fetal abnormalities have occurred</td>
</tr>
</tbody>
</table>

Transfer of Medications into Milk

- Concentration gradient
- Passive diffusion
  - Non-ionized
  - Non-protein bound
  - Low molecular weight
- Drug exposure to the baby
  - More quantity of drug in mother = more drug in baby
  - Amount consumed

Lactation Risk Categories

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
</tr>
<tr>
<td>L2</td>
</tr>
<tr>
<td>L3</td>
</tr>
<tr>
<td>L4</td>
</tr>
<tr>
<td>L5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safest: no observed increase in ADRs in the infant; controlled studies failed to demonstrate risk</td>
</tr>
<tr>
<td>Safer: studied in limited number of breastfeeding women; evidence of risk is remote</td>
</tr>
<tr>
<td>Moderately safe; no controlled studies in breastfeeding women; only give drug if benefit outweighs risk</td>
</tr>
<tr>
<td>Possibly hazardous; positive evidence of risk to breastfed infant, benefits must outweigh risk</td>
</tr>
<tr>
<td>Contraindicated; studies have demonstrated significant risk to the infant</td>
</tr>
</tbody>
</table>

Minimizing Risk to Nursing Infants

- Avoid drug therapy when possible
- Use topical therapy
- Safety in pregnancy is NOT = safe during breastfeeding

- Ideal Medications
  - Shortest half-life
  - Studies well in infants
  - Poor oral absorption
  - Low lipid solubility
- When to give medications?
  - Single daily dose prior to longest sleep interval
  - Feed prior to dose (multiple daily doses)
  - “Pump & Dump”

Outline

- Drug Disposition & Dosing
- Pregnancy & Lactation
- Neonates & Infants
- Children & Adolescents
- Medication Administration Issues in Pediatric Patients
- Medication Related Problems
- Safe Medication Practices & Recommendations
Neonatal & Pediatric Definitions

<table>
<thead>
<tr>
<th>Gestational Age (GA)</th>
<th>Weeks from 1st day of mother’s last menstrual period = # of days in utero</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnatal Age</td>
<td>Chronological age since birth</td>
</tr>
<tr>
<td>Neonate</td>
<td>Up to 1 month after birth</td>
</tr>
<tr>
<td>Infant</td>
<td>1 month – 2 years</td>
</tr>
<tr>
<td>Child</td>
<td>2 years – &lt;12 years</td>
</tr>
<tr>
<td>Adolescent</td>
<td>12 years – 21 years</td>
</tr>
<tr>
<td>Adult</td>
<td>&gt; 18 years</td>
</tr>
</tbody>
</table>

Pharmacokinetic Properties During Development

Absorption
- Percutaneous Absorption
  - Enhanced in Neonates
  - Epidermal perfusion & hydration
  - Stratum corneum
  - BSA : Weight
- Muscle/SQ Tissue
  - Decreased in preterm infants

Distribution
- Increased extracellular & total body water
- Increased Vd in neonates
- Plasma proteins
  - Decreased in neonates
  - Affects highly protein bound drugs
- Blood Brain Barrier

Neonatal Weight Specific Definitions

- Normal birth weight:
  - ~2500 gm – 4000 gm (1.13 lb – 1.8 lb)
- Low birth weight (LBW)
  - <2500 gm (1.13 lb)
- Very low birth weight (VLBW)
  - <1500 gm (0.68 lb)
- Extremely low birth weight (ELBW)
  - <1000 gm (0.45 lb)
Metabolism

- Phase I Enzyme System
  - Premies: 25-50% of adult function
  - Up to 7 months: 50-70% of adult function
  - Oxidation
    - Birth: 33-50% of adult function
    - At 1 year: 2-5x of adult function
  - Hydrolysis
    - Decreased in premies and neonates
    - Adult function by 1 year

- Phase II Enzyme System
  - Acetylation
    - By 6 months = adult function
  - Glucuronidation
    - By 12-18 months = adult function
  - Sulfonation
    - > adult function in infancy & early childhood
  - Methylation
    - > adult function in infancy & early childhood

Renal Elimination

- Nephrogenesis
- Function decreased in preterm infants
- Glomerular Filtration & Tubular functioning
- Improves with age
- Serum Creatinine (SCr)
  - Birth level reflective of Mom
  - Decreases over 1-2 weeks to baseline values 0.3-0.5 mg/dL
  - CrCl = k x length (cm) / SCr

Urine Output

- Normal urine output
  - Neonates, Infants and Toddlers 2-3 ml/kg/hour
  - Preschool and school age 1-2 ml/kg/hour
  - School age and adolescent 0.5-1 ml/kg/hour
- Minimal urine output
  - Neonates, Infants and Children (<30 kg) 1 ml/kg/hour
  - Older Children and adolescents (30-60 kg) 0.5 ml/kg/hour
  - Children weighing (> 60 kg) 30 ml/hour

Normal SCr Ranges

<table>
<thead>
<tr>
<th>Age</th>
<th>SCr (mg/dL)</th>
<th>Range (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature &lt; 2 weeks</td>
<td>0.9</td>
<td>0.7 – 1.4</td>
</tr>
<tr>
<td>Premature ≥ 2 weeks</td>
<td>0.8</td>
<td>0.7 – 0.9</td>
</tr>
<tr>
<td>Term neonate &lt; 2 weeks</td>
<td>0.5</td>
<td>0.4 – 0.6</td>
</tr>
<tr>
<td>Term neonate ≥ 2 weeks</td>
<td>0.4</td>
<td>0.3 – 0.5</td>
</tr>
<tr>
<td>2 weeks – 5 years</td>
<td>0.4</td>
<td>0.2 – 0.5</td>
</tr>
<tr>
<td>5 – 10 years</td>
<td>0.6</td>
<td>0.3 – 1</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>0.9</td>
<td>0.6 – 1.4</td>
</tr>
</tbody>
</table>

Measurements of Renal Function/CrCl

- Urine output
- BUN, serum creatinine
- GFR = most precise measurement of renal function
- Often impractical to use for routine assessment
- Schwartz Equation – preferred in pediatrics for estimation of CrCl

- Schwartz Equation
  - Need patient’s height
  - $CL_{cr} (ml/min/1.73m^2) = \frac{k \times ht(cm)}{SCr}$
  - k (age-dependent constant)
    - 0.33 for pre-term infant – 1 yr
    - 0.45 for full-term infant – 1 yr
    - 0.55 for children from 2-12 yr
    - 0.55 for female from 13-21 yr
    - 0.7 for male from 13-21 yr
    - 0.413 for chronic kidney disease, renal transplant
Outline
- Drug Disposition & Dosing
  - Pregnancy & Lactation
  - Neonates & Infants
  - Children & Adolescents
- Medication Administration Issues in Pediatric Patients
- Medication Related Problems
- Safe Medication Practices & Recommendations

Dosing in Pediatric Patients

- mg/kg/day
- mg/kg/dose
- mg/m²
- Age
- Pharmacokinetic monitoring

BSA vs. Weight Calculation Example

- 8 month old child receiving chemotherapy
  - Weight = 9 kg
  - Height = 70 cm
  - BSA = 0.42

- Dosing of 500 mg/m² for ≥ 12 kg or 16.6 mg/kg for < 12 kg

- BSA dosing method: \(500 \text{ mg} \times 0.42 = 210 \text{ mg}\)
- Weight dosing method: \(16.6 \text{ mg} \times 9 = 149 \text{ mg}\)

Dosing in Pediatric Patients

- Dosing Intervals Differences
  - Differ between children, adolescents, adults
- Disease States affecting clearance
  - Hepatic impairment
  - Renal impairment
  - GI Disease
  - Cystic Fibrosis
  - Cancer
### Outline

- Drug Disposition & Dosing
  - Pregnancy & Lactation
  - Neonates & Infants
  - Children & Adolescents
- Medication Administration Issues in Pediatric Patients
  - Medication Related Problems
  - Safe Medication Practices & Recommendations

### Medication Administration

#### Preferred Dosage Forms in Children
- Can the child swallow pills?

#### Other alternatives?
- Crushing Tablets (some)
- Opening Capsules
- Chewable tablets
- Solutions/Suspensions
  - Availability?

#### Medication Administration

- Oral Osmolarity
  - \(< 600 \text{ mOsm/kg}\)
- IV Peripheral vs. Central Osmolarity
  - Peripheral IV (PIV)
    - \(< 1000 \text{ mOsm/L}\)
    - Maximum D12.5W
  - Central IV (CIV)
    - Maximum D30W
- Effects of Hyperosmolarity
  - Necrotizing Enterocolitis (Oral)
  - Intraventricular Hemorrhage (IV)

### Medication Administration

- Avoidance of certain preservatives/additives
  - Sorbitol
    - Diarrhea, abdominal pain, flatulence
  - Sodium benzoate
    - Displaces bilirubin
  - Benzyl alcohol
    - "Gasping syndrome"
  - Propylene glycol – neonates
    - Serum hyperosmolality, lactic acidosis, hypotension, arrhythmias, CNS/respiratory depression, death

### Medication Administration

- Alternative Routes of Administration
  - IM/SQ
    - Limited to particular volumes, painful
  - Rectal
  - Nasal/Buccal
  - Inhalation
  - IV
    - Fluid overload issues – watch concentrations, volumes
    - Delivery systems must be able to deliver small volumes

### Administering Medications to Children

- Use a syringe
  - Squirt between cheek and gum in portions
  - Not front of mouth
  - Not squirt to the back of the throat
- Liquids
  - Flavoring - Cherry/Grape, Flavor RX
  - Good flavored item afterwards
  - Water, juice, foods they like
- Crushing Tabs/Opening capsules
  - Place on small amount of soft foods
  - Pudding, applesauce, yogurt
  - Strong flavors = better covering agents
  - Peanut butter, Jam (not jelly), chocolate syrup
Outline

- Drug Disposition & Dosing
  - Pregnancy & Lactation
  - Neonates & Infants
  - Children & Adolescents
  - Medication Administration Issues in Pediatric Patients
- Medication Related Problems
- Safe Medication Practices & Recommendations

Medication Related Problems in Kids

- Adverse Drug Reactions (ADRs)
- Drug Interactions
- Therapeutic Duplication
- Inappropriate Drug Selection
- Subtherapeutic Dosing
- Overdose/Toxicity
- Drug Use without and Indication
- Omission of Medication

Risk of ADR Increased in Younger Children

- Immaturity
- Lack of information
- Need to compound extemporaneous formulations
- Need for calculations in all aspects of medication process
- Ease of overdose with concentrated/narrow therapeutic index medications
- Adverse drug events unique to children
- Adverse effects of additives in medication formulations
- Nonadherence

Pharmacokinetic Issues Related to ADRs

- Lower levels of plasma proteins = higher unbound concentrations = toxicity
- Decreased renal function
- Decreased hepatic enzyme activity
- Increased skin permeability

Medication Errors

- Medication errors most common type of medical error and cause of preventable adverse events
- Any preventable event that occurs in the process of ordering or delivering a medication, regardless of whether an injury occurred or the potential for injury was present
- Potential to cause significant harm in pediatric population at a higher rate than in adults

Extent of Problem

- Adults
  - Reported incidence ranges 1 - 30% of hospital admissions or 5% of written orders
- Pediatrics
  - Up to 1 in 6.4 written orders
  - Retrospective review of pediatric medication errors in MER program and MedMarx database from 1995 – 1999
  - ~48,000 error records
  - Significantly greater rate of medication errors resulting in harm or death in pediatric patients compared to adults (31% vs. 13%)

Extent of Problem - Pediatrics

• Prospective 2-institution cohort study of 1120 pediatric patients over 6 week period
  • Goals
    • Determine rates of medication errors, potential ADEs and ADEs
    • Compare to previous literature, analyze the type of errors, potential impact of prevention strategies
    • 10,778 orders, 616 medication errors (5.7%)
    • 26 ADEs (0.24%), 19% were preventable
    • 115 potential ADEs
    • Potential ADEs occur in pediatric patients 3 times more often compared to adults
    • Neonates experienced higher medication errors (via subgroup analysis) and overall greater potential ADE rates (p<0.001)

Kaushal et al.  Medication Errors and Adverse Drug Events in Pediatric Inpatients
JAMA 2001; 285:2114-2120

Extent of Problem - Pediatrics

• USP MedMarx Database 2006 - 2007
  • ~2.5% of Pediatric Medication Errors led to patient Harm
  • Most common errors:
    • Improper dose/quantity
    • Omission error
    • Unauthorized/Wrong drug
    • Prescribing Error


Why are Children at Greater Risk?

• Medication formulation and packaging
• Most health care settings primarily built around the needs of adults
• Ability to tolerate medication errors due to differences in pharmacokinetics and pharmacodynamics
• Dosing errors more detrimental
• Inability to communicate effectively about adverse effects
• FDA labeling lacking for pediatric population

TOP 10 Causes of Pediatric Errors

• Performance deficit
• Knowledge deficit
• Procedure/Protocol not followed
• Miscommunication
• Inaccurate or Omitted Transcription

• Improper Documentation
• Drug Distribution System Error
• Calculation Error
• Computer Entry Error
• Lack of System Safeguards


Outline

• Drug Disposition & Dosing
  • Pregnancy & Lactation
  • Neonates & Infants
  • Children & Adolescents
  • Medication Administration Issues in Pediatric Patients
  • Medication Related Problems
  • Safe Medication Practices & Recommendations

Risk Reduction Strategies

• Standardize and identify medications effectively, as well as the processes for drug administration
  • Maintain pediatric formulary with policies for drug evaluation, selection, and therapeutic use
  • Prevent timing errors – standardize protocol days
  • Limit concentrations and dose strengths of high alert medications
  • Ensure compounded medications are similar between outpatient and inpatient
  • Use oral syringes for preparation and administration of oral medications
Risk Reduction Strategies

• Ensure full pharmacy oversight—as well as the involvement of other appropriate staff—in the verifying, dispensing and administering of both neonatal and pediatric medications
  - Assign pediatric trained practitioners to any committee responsible for oversight of medication management
  - Provide up-to-date pediatric specific information
  - Orient all pharmacy staff to specialized neonatal/pediatric services in organization

• Pharmacy Oversight Continued
  - Provide dose calculation sheets for emergency and commonly used medications for all ICU patients
  - Develop preprinted order forms – create standardized areas for wt, allergies, prescriber name, sig, contact
  - Create pediatric satellite pharmacies or assign pharmacists and technicians with pedi experience to NICU, PICU, Oncology Units
  - Separate storage and preparation of pediatric medications from adults

Risk Reduction Strategies

• Use technology judiciously
  - Use methods to ensure accuracy of technology that measures and delivers additives for IV solutions
  - Use dose and dose range checking software
  - Limit medications in automated dispensing cabinets that do not have appropriate pharmacist review
  - Utilize and provide appropriate education for smart pumps
  - Use consistent physiological monitoring for children under sedation or during procedures
  - Develop bar coding with pediatric capability

Medication Reconciliation in the Continuum of Care

• Joint Commission NPSG.03.06.01 – Existing Requirement
  - Obtain information on the medications the patient is currently taking when he or she is admitted to the hospital or is seen in an outpatient setting.
  - Define the types of medication information to be collected in non–24-hour settings and different patient circumstances
  - Compare the medication information the patient brought to the hospital with the medications ordered for the patient by the hospital in order to identify and resolve discrepancies.

• Joint Commission NPSG.03.06.01 (Continued)
  - Provide the patient (or family as needed) with written information on the medications the patient should be taking when he or she is discharged from the hospital or at the end of an outpatient encounter (for example, name, dose, route, frequency, purpose)
  - Explain the importance of managing medication information to the patient when he or she is discharged from the hospital or at the end of an outpatient encounter.
**Additional Recommendations**

- Weigh all pediatric patient upon admission, use standard measurements – kg
- Weight based dosing
  - No high-risk drug should be dispensed or administered if pediatric patient has not been weighed unless emergency
- Use pediatric specific formulations and concentrations whenever possible
  - If not possible prepare and dispense in patient specific unit dose or unit of use containers instead of adult unit doses
- Ensure comprehensive specialty training in pediatrics
  - Provide an adequate number of trained RN/RPh staff

**Additional Recommendations**

- Clearly differentiate (from adult formulations) all products that have been repackaged for use in pediatric populations
  - Use clear, highly visible warning labels
  - Keep concentrated adult products away from pediatric unit, avoid storage in same automated dosing cabinet
  - Communicate verbally and in writing information about the child’s medications to caregivers
  - Have pharmacist with pediatric experience available or on-call at all times
  - Establish medication procedures that include pediatric prescribing and administration practices

**Keeping your child safe**

- Know your child’s weight
- Always read the labels on medications
  - Clearly understand how much to give and how often
  - Know the mg dose AND mL dose
- Know the active ingredient and concentrations of your child’s medications
- Give the correct formulation for your infant/child/adolescent and correct amount
- Talk to your doctor, nurse, or pharmacist to find out what is or not safe to mix with medications
- Keep list of ALL medications
  - RX, OTC, Herbal/Dietary Supplements

**Questions??**

- Use child resistant caps
- Store all medications in a safe place
- Use the dosing tool that comes with the medication only for that medication
- Know the difference between a teaspoon and a tablespoon – safer to use syringes for measurement
- Know the concentrations of your child’s medications
  - Take a picture
  - Bring them along to ALL doctor visits
  - Have a typed up list